REMARKS

Upon entry of this amendment, claims 1-5, 8, 10, and 28-40 constitute the pending claims in the present application. Applicants have canceled claims 6, 7, and 11-27, which are directed to non-elected inventions. Applicants reserve the right to prosecute claims of similar or identical scope in future applications. Claims 1-5, 8, 10, and new claims 28-40 are directed to the elected Group I invention. Support for the new claims can be found throughout the specification, including the originally filed claims.

Applicants note that the Examiner has decided to search SEQ ID NOs: 4, 6, and 8 as well as all primers represented by SEQ ID NOs: 12-15.

Applicants note that the IDS has been considered by the Examiner, with the exception that reference BH on the Form PTO-1449, filed 7/22/02, has been struck through because the Examiner cannot identify the reference based on the information on the IDS.

The Office Action points out certain inconsistencies found in the Oath / Declaration, which is a copy of the Oath / Declaration of the parent application U.S.S.N. 08/448,371. Applicants have submitted a supplemental ADS (Application Data Sheets) in accordance with 37 CFR 1.76(c) to correct these defects. Pursuant to 37 CFR 1.76(d), ADS governs inconsistencies in domestic and foreign priority claims between an earlier filed Oath / Declaration and a later filed ADS.

The Office Action further asserts that the title of the invention is not descriptive, and requests Applicants to provide a more appropriate title. Applicants have amended the specification to change the title according to the Examiner's suggestion.

The Office Action objects to the specification since reference to PCT/US95/05467 was not recited in the first line of the specification. Applicants have submitted the above-referenced supplemental ADS to provide the necessary domestic and foreign priority claims pursuant to 37 CFR 1.76(b). In addition, Applicants have amended the first paragraph of the specification to repeat the information already supplied in the supplemental ADS.

The Office Action also objects to the specification since no SEQ ID NO. is recited on page 11, line 29. Applicants have amended the specification to obviate this objection. Applicants submit that no new matter is introduced, because the text obviously refers to the OP-1 protein

sequence, which is set forth in SEQ ID NO: 10. Reconsideration and withdrawal of the objections are respectfully requested.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim objections

The Office Action objects to claims 1, 2, and 8, and suggests removing one of the commas after "(ALK-6)." Accordingly, Applicants have amended the claims to obviate this objection. Applicants have also amended the claims to uniformly use "OP-1" instead of "OP1." Applicants submit that there is no narrowing of scope due to these amendments.

The Office Action also objects claim 5 for reciting "any of claims 1-4." Accordingly, Applicants have adopted the Examiner's suggestion and amended claim 5 to obviate this objection. Reconsideration and withdrawal of the objections are respectfully requested.

Claim rejections under 35 U.S.C. 112, first paragraph – scope of enablement

Claims 1-5, and 8-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for method of identifying binding analogs which interact with the claimed fragments of SEQ ID NO: 4, 6, and 8, does not reasonably provide enablement for methods of identifying binding analogs of proteins which are at least 40% identical to residues 23-132 of SEQ ID NO: 8, or any polypeptide chain which is amplified by the primers of SEQ ID NO: 12-15, or which hybridizes to residues 256-552 of SEQ ID NO: 8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Specifically, the Office Action cites the Wands factors from *In re Wands, 8 USPQ 2d, 1400* (CAFC, 1988), and asserts that the breadth of the claims is excessive with regard to claiming methods of identifying binding analogs of: a) proteins at least 40% identical to residues 23-132 of SEQ ID NO: 8, or b) proteins encoded by polynucleotides amplified by primers 12-15, or c) proteins encoded by polynucleotides that hybridizes to residues 256-552 of SEQ ID NO: 8. The Office Action contends that the specification does not teach a skilled artisan how to make a protein at least 40% identical to residues 23-132 of SEQ ID NO: 8 yet still retain the ability to bind OP-1, thus the specification has not enabled a skilled artisan to use these proteins for the

claimed screening method. The Office Action further alleges that the specification does not provide examples or guidance for making such proteins, and it is not predictable for a skilled artisan to make a functional ALK protein other than SEQ ID NOs: 4, 6, or 8.

Applicants submit that the arguments of the Office Action are based on a mis-interpretation of the case law. In fact, according to the CAFC ruling in *In re Wands*, Applicants submit that the scope of the claimed invention is fully enabled for the reasons that follow.

Jack Wands *et al.* claimed methods for the immunoassay of HBsAg by using high-affinity monoclonal IgM antibodies. The PTO Board finally rejected the broadest claim on grounds of lack of enablement. Specifically, the sole issue was whether it would require undue experimentation to produce high-affinity IgM monoclonal antibodies with the recited avidity ("having a binding affinity constant for said HBsAg determinants of at least 10^9 M^{-1}").

The undisputed facts of the case are: Wands made 10 fusions, the first four of which were unsuccessful due to technical problems and inexperience. The next 6 fusions before filing and the 11^{th} fusion after filing were all successful. From among the 6 successful fusions, they screened and obtained 143 so-called "high-binding hybridomas," which secrete antibodies that bind the antigen (HBsAg) with at least 10,000 cpm in the commercial RIA assay used by Wands. From these 143 hybridomas, they screened 9 and froze the remaining 134. Among the 9 hybridomas screened, they found that 4 were actually IgM monoclonal Abs that fall within the scope of the claim, 3 were found to be IgG monoclonal antibodies (outside the scope), and the remaining 2 were also IgM Abs, but were not tested for binding constants.

The PTO board held that only 4 out of 143 hybridomas were within the scope of the claim, and thus concluded that a skilled artisan would require undue experimentation to make the IgM antibody required to practice the claimed method. The CAFC, however, ruled that "the board's interpretation of the data is erroneous. ... The PTO's position leads to the absurd conclusion that the more hybridomas an applicant makes and saves without testing, the less predictable the applicant's results become."

Applicants note a striking parallelism between the Wands fact pattern and the claimed invention. First of all, Wands claimed an assay method using a specific kind of antibody with a desired functional feature (a binding affinity constant for the antigen of at least 10^9 M^{-1}). The present application claims an assay method using a few specific kinds of receptors with a desired

functional feature (a polypeptide chain having binding affinity for OP-1 and sharing at least 40% amino acid identity with residues 23-122 of ALK-6; encoded by a nucleic acid obtainable by amplification with one or more primer sequences defined by SEQ ID NOs: 12-15; or encoded by a nucleic acid that hybridizes under stringent conditions with a nucleic acid comprising the sequence defined by nucleotides 256-552 of ALK-6). In fact, the subject peptides of the claimed invention are not purely defined by function, but rather defined by function correlating to structure.

Secondly, the Wands method uses IgM, which can be made through a well-known process (monoclonal antibody generation) by screening large amounts of candidate antibodies, for a specific subset of antibodies with the desired function. The presently claimed method uses, for example, a polypeptide of claim 1(iv), which can be made through another well-known process (combinatorial random mutagenesis) by screening large numbers of randomly mutated candidate polynucleotides for a specific subset of polynucleotides encoding proteins with the desired function (binds OP-1 and at least 40% identical to residues 23-122 of SEQ ID NO: 8). In other words, contrary to the contentions of the Office Action, Applicants need not tell a skilled artisan which 60% of the above-referenced sequence can be mutated to what amino acids, yet still retain the ability to bind OP-1. Combinatorial mutagenesis coupled with functional screening is simply much faster and efficient in generating the desired polynucleotides. To say that Applicants have only identified SEQ ID NOs: 4, 6, and 8 that bind OP-1, and that Applicants have provided no guidance or working examples other than those of ALK-2, -3, and -6, is analogous to saying that Wands had only identified four IgM antibodies falling within the scope of the claimed methods, and that Wands had provided no guidance or working examples other than those 4 identified IgM antibodies.

For the same reason, Applicants submit that PCR amplification using primers of known sequences was a routine and well-known process in the art of molecular biology at the time of filing. Coupled with a functional screen of OP-1 binding, a skilled artisan would have been able to make the polypeptide of claim 1(v) without undue experimentation.

Similarly, Applicants submit that high stringency hybridization using a known probe sequence was a routine and well-known process in the art of molecular biology at the time of

filing. Coupled with a functional screen of OP-1 binding, a skilled artisan would have been able to make the polypeptide of claim 1(vi) without undue experimentation.

All these techniques for making the subject polypeptides were well known as of the filing date of the instant application. Pursuant to MPEP 2164.01, "A patent need not teach, and preferably omits, what is well known in the art."

In addition, since ALK-6 and ALK-3 are 46% identical in the ligand-binding domain (see page 7, 1st full paragraph), it is conceivable that an ALK-3 homolog / derivative that is 99% identical to ALK-3 could be just 45% identical to the reference sequence ALK-6. Since ALK-3 binds OP-1, this putative derivative "ALK-3" would be highly likely to bind to OP-1.

Therefore, Applicants submit that the claimed invention is fully enabled for the kinds of polypeptides that can be used for the method.

Nevertheless, Applicants have submitted new dependent claims 32-40 to expedite prosecution and to further clarify the subject matter claimed. Applicants submit that at least these dependent claims fulfill the enablement requirement, as the instant Office Action acknowledges.

The Office Action further alleges that Applicants have not enabled the scope of cellular response recited in claim 2.

Applicants submit that numerous OP-1-mediated cellular and biological responses were known at the time of filing. Pursuant to MPEP 2164.01, "A patent need not teach, and preferably omits, what is well known in the art." Regardless, the instant specification has meticulously set forth a number of OP-1 mediated cellular responses (see, for example, Example 9) which can all be employed to practice the claimed assay. For example, excluding the ones already recited in claim 3, OP-1 also induces Alkaline phosphatase activity, PTH-mediated cAMP production, or a reporter gene in operable association with a OP-1-responsive promoter (such as the PAI-1 promoter described in Example 9). A skilled artisan could easily identify, among the rich literature resulting from more than a decade of OP-1 related research, other OP-1-mediated biological responses without undue experimentation.

Thus Applicants submit that the pending claims as amended fully satisfy the enablement requirement of 35 U.S.C. 112, first paragraph. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim rejections under 35 U.S.C. 112, first paragraph – written description

Claims 1-5, and 8-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the Office Action asserts that the claimed invention encompasses a genus of polypeptide sequences, such as polypeptides at least 40% identical to a defined fragment of ALK-6, polypeptides encoded by polynucleotides that hybridize under stringent conditions with a defined sequence, etc. Thus, the Office Action asserts that structural features that distinguish the claimed genus of polypeptides from other polypeptides are lacking from the disclosure. The Office Action further asserts that because there are no common structural attributes that identify the members of the genus, and the genus is highly variant, the disclosed few SEQ ID NOs. are not sufficient to describe the whole genus, and the Applicants do not have possession of the claimed invention.

Applicants submit that the several genera of the polypeptides (40% identical to ALK-6, encoded by polynucleotide amplified by primers, and encoded by a polynucleotide obtained by high stringency hybridization) all meet the written description requirement.

First of all, Applicants wish to direct the Examiner's attention to Example 9 of the "Revised Interim Written Description Guidelines Training Materials" published on the USPTO website (a copy of Example 9 is submitted herewith as **Exibit A**). In Example 9 of the Guidelines, the hypothetical claim is directed to a genus of nucleic acids, all of which must hybridize with SEQ ID NO: 1, and must encode a protein with a specific activity. Since the hypothetical SEQ ID NO: 1 is novel and fully disclosed, and falls within the scope of the hypothetical claim, the single species meets the written description requirement. As to the genus claim, the Guidelines further elaborates that "a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Thus a representative number of species is disclosed...and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention." the Guidelines' conclusion: The claimed invention is adequately described.

In accord with that analysis, the subject polypeptide as defined in the claims must also be encoded by a nucleic acid that must hybridize with nucleotides 256-552 of SEQ ID NO: 8 under high stringency conditions. The encoded polypeptide must also have a specific activity (bind to OP-1). Thus, such embodiments of the subject polypeptides are fully described under the standard of the Guidelines.

Similarly, although the Guidelines does not have an example for nucleic acids obtained by amplification using defined primers, Applicants submit that the same logic applies in this situation. Specifically, a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the amplification process inherently yields structurally similar DNAs – the primers must be able to hybridize to the template to be able to amplify the target. In fact, in certain amplification processes such as PCR, the hybridization of the primers to the template DNA (at the annealing sites for the primers) must be highly stringent, since the primer-template hybrid must be able to withstand the usual 72 °C polymerase extension temperature without falling apart. Thus, at the primer annealing sites, the match between the primers and the template must be identical or nearly identical. Also, both primers in the amplification pair must anneal simultaneously to the template for the amplification to work. In a sense, this is even more stringent than high stringency hybridization. Since at least one polypeptide is encoded by a nucleic acid falling within the scope, a representative number of species are disclosed, and the level of skill and knowledge in the art are adequate to determine that Applicants are in possession of the claimed invention.

Lastly, polypeptide sequences sharing at least 40% sequence identity to residues 23-122 of SEQ ID NO: 8 and binding OP-1 can be analogized to Example 13, claim 2, of the above-referenced Guideline. There is a key difference between the instant claimed invention and the "variant" claim in Example 13. The instant claimed invention sets forth distinguishing functional and structural attributes shared by all members of the subject genus – at least 40% identical to residues 23-122 of SEQ ID NO: 8, and binding to OP-1. Such distinguishing attributes are missing in the generic "variant claim" of Example 13, which "do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions." While the lack of such common attributes renders the variant claim without proper written description, Applicants submit that the instant specification discloses at least three members that fall within the scope of

the claim. These distinct species are different enough to represent the full range of polypeptides falling within the scope of the claims. Thus a representative number of species are disclosed, and the level of skill and knowledge in the art are adequate to determine that Applicants are in possession of the claimed invention.

The Office Action further contends that Applicants have not adequately described all of the potential cellular responses recited in claim 2, and that Applicants have only identified a small number of cellular responses for measuring the effect of a binding analog.

Applicants submit that many other OP-1 mediated cellular responses were well known in the art at the time of filing. The instant specification describes the following as exemplary OP-1-mediated cellular responses: ligand-induced receptor autophosphorylation (pages 32-34 in Example 5); ligand-induced reporter gene activation (page 34 in Example 5, also see page 50 of Example 9.2); expression of osteoblast differentiation markers such as Alkaline Phosphatase, PTH-mediated cAMP and osteocalcin (pages 47-50 of Example 9.1); and inhibition of epithelial cell proliferation (page 51 of Example 9.3). The art also describes the following OP-1-mediated cellular responses: expression of NCAM and L1 (Perides *et al.*, *J Biol Chem* **269(1)**:765-70, Jan. 7, 1994), expression of type-I collagen (Maliakal *et al.*, *Growth Factors* **11(3)**: 227-34, 1994), induction of endochondrial bone formation (Asahina *et al.*, *J Cell Biol* **123(4)**: 921-33, Nov. 1993); alcian blue staining at pH 1 (Asahina *et al.*, *J Cell Biol* **123(4)**: 921-33, Nov. 1993), and types II, IX and X collagens expression (Asahina *et al.*, *J Cell Biol* **123(4)**: 921-33, Nov. 1993). Pursuant to MPEP 2164.01, "A patent need not teach, and preferably omits, what is well known in the art." Therefore, Applicants should not be unduly burdened to enumerate a laundry list of known OP-1-mediated cellular responses. In addition, any later-developed OP-1-mediated cellular responses also fall within the scope of the claimed invention according to *In re Hogan* 559 F.2d 595, 604, 194 USPQ 527, 535 (CCPA 1977).

Based on the above-arguments, Applicants submit that all pending claims meet the written description requirement of the first paragraph of 35 USC 112. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections under 35 U.S.C. 112, second paragraph

Claims 1-5 and 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Office Action asserts that claims 1-5 and 8-10 are incomplete (lacking a conclusion step) and suggests correction. Applicants have adopted the Examiner's suggestion and amended method claims 1 and 2 to obviate this rejection. Applicants also submit that claim 8 is a kit claim, not a method claim. Thus, a conclusion step would not be necessary for claim 8 and its dependent claims.

The Office Action rejects claims 1, 2, and 8 as confusing since the metes and bounds of "substantially the same binding affinity" are unknown.

Pursuant to MPEP 2173.05(b), certain relative claim terminologies are permitted: "Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification. When a term of degree is present, determine whether a standard is disclosed or whether one of skill in the art would be apprised of the scope of the claim. When a term of degree is present in a claim, first a determination is to be made as to whether the specification provides some standard for measuring that degree."

Based on this criterion, Applicants submit that the specification clearly sets forth the standard to measure the degree of affinity, using the well-known art-accepted dissociation constant K_d. For example, the instant specification has described in several occasions the relative affinity of bindings between the subject ligands and receptors and their measurement standard K_d (See, for example, page 7, first full paragraph). Thus, Applicants submit that a skilled artisan would understand the meaning of the term "substantially the same" in view of the common knowledge of the art and the instant specification.

This standpoint is further consistent with the same MPEP section, which particularly listed the use of the word "substantially" as being definite if a skilled artisan would be reasonably appraised of the meaning of the term, especially in view of the guidelines set forth in the specification: "[t]he term 'substantially' is often used in conjunction with another term to describe a particular characteristic of the claimed invention. It is a broad term. *In re Nehrenberg*,

280 F.2d 161, 126 USPQ 383 (CCPA 1960). The court held that the limitation 'to substantially increase the efficiency of the compound as a copper extractant' was definite in view of the general guidelines contained in the specification. *In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975). The court held that the limitation 'which produces substantially equal E and H plane illumination patterns' was definite because one of ordinary skill in the art would know what was meant by 'substantially equal.' *Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988)." Thus reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1, 2, and 8, parts (i) – (iii) are rejected as confusing since ALK-6 is an OP-1 receptor, and it is not clear what is meant by "or an OP-1-binding analog thereof."

Applicants submit that a skilled artisan would understand that "an OP-1 binding analog thereof" means a receptor analog of ALK-2, -3 or -6, which binds OP-1. Nevertheless, Applicants have amended the claims to further clarify the subject matter claimed. No new matter was introduced, and there is no narrowing of scope due to these amendments.

Claims 1, 2, and 8 are rejected as being vague for reciting "stringent conditions." The Office Action requests Applicants to introduce exact hybridization conditions into the claims.

Applicants respectfully traverse this rejection, because the term "stringent conditions" is supported in the specification and is well understood in the art to encompass conditions of hybridization which allow hybridization of structurally related, but not structurally dissimilar, nucleic acids. The term "stringent" is a term of art which is understood by the skilled artisan to describe any of a number of alternative hybridization and wash conditions which allow annealing of only highly complementary nucleic acids.

In particular, the specification describes stringent hybridization conditions on page 8, 1st full paragraph. The paragraph refers to the most used laboratory manual "Molecular Cloning" for further details of the conditions. The paragraph also sets forth one exemplary such condition as "hybridization in 40% formamide, 5×SSPE, 5×Denhardt's Solution, and 0.1% SDS at 37°C. overnight, and washing in 0.1×SSPE, 0.1% SDS at 50°C." As a skilled artisan would appreciate, many equivalent protocols exist and several popular molecular cloning manuals describe suitable conditions for stringent hybridization and, furthermore, provide formulas for calculating the length of hybrids expected to be stable under these conditions (see e.g. *Current Protocols in*

Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6 or 13.3.6; or pages 9.47-9.57 of Sambrook, *et al.* (1989) *Molecular Cloning*, 2nd ed., Cold Spring Harbor Press). This is also consistent with the MPEP section recited above, which states that a claim terminology reciting a degree is not indefinite if the specification sets forth how the degree is to be measured (supra). Thus, the term "stringent" is not indefinite, but rather a functional description of many equivalent variations in salt and temperature conditions. Indeed it is well understood that there are many functionally equivalent methodologies for achieving stringent conditions. Each of these methodologies involves a number of interrelating variables such as the selection of hybridization membrane composition, hybridization buffer composition, hybridization buffer temperature, wash buffer composition, and wash buffer temperature. The skilled artisan recognizes that many of these factors interrelate. For example, the correct temperature for a stringent hybridization will depend upon the chemical composition of the hybridization buffer (68 °C for aqueous buffers versus 42 °C for buffers containing 50% formamide), and the selection of hybridization buffer conditions will depend upon the composition of the membrane used (nitrocellulose versus nylon) (see Sambrook, *et al.* (1989) *Molecular Cloning*, 2nd ed., Cold Spring Harbor Press). Therefore, in view of the specification, Applicants respectfully submit that the metes and bounds of the claimed subject matter has been clearly set forth and one of skill in the art would readily appreciate the scope of the claim. To limit the claimed method to just one specific hybridization condition would unduly restrict the scope of the claimed invention, and allow a potential infringer to easily "engineer around" the claimed invention without any inventive step or undue experimentation. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 2 and 9 are rejected as being confusing since it is unclear what "cellular response" is being measured in part (c) of the claims. The Office Action asserts that Applicants have only enabled the assays recited in claim 3.

Applicants submit that the Office Action has confused the enablement requirement of 35 USC 112, first paragraph, with 35 USC 112, second paragraph. Even assuming, for the sake of argument, that Applicants had not enabled any cellular responses (which Applicants traverse, as argued above) other than the ones recited in claim 3, Applicants submit that the meaning of the term "cellular response" itself is clear (see below). Pursuant to MPEP 2173.04, "[b]readth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA

1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph."

Applicants submit that "cellular response," when used in the context of the claims, clearly means a cellular response resulting from OP-1-mediated signal transduction. The Office Action fails to point out what embodiment might or might not fall within the scope of the claimed invention if the term "cellular response" is used, thus a rejection under 35 USC 112, second paragraph, appears to be improper. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 4, 5, and 10 are rejected as being confusing since the purpose of the reporter gene, the control element, or the additional type II receptor are allegedly unclear.

Applicants submit that a skilled artisan looks to the specification to understand how to make and use the invention. Despite the relatively high level of skill in the art regarding the use of promoters and reporter genes, the instant specification has nevertheless set forth the details of how to use OP-1-responsive promoters and reporter genes to measure OP-1-mediated cellular response (see page 34 in Example 5, also see page 50 of Example 9.2). Therefore, a skilled artisan would readily understand the metes and bounds of the claimed invention in claim 4. Applicants have nevertheless amended the claim to further clarify the subject matter claimed. Similarly, the specification has described in detail in Example 8 that certain OP-1 receptors need a Type II receptor for binding OP-1 like morphogens, while certain other receptors do not need such a Type II receptor for OP-1 binding. The skilled artisan would not be confused as to the metes and bounds of the claimed invention.

Claim 5 is rejected as being indefinite for lacking antecedent basis when using the term "sample." Applicants have amended claim 5 to obviate this rejection. Antecedent basis for the newly inserted "surface receptor protein" is found in claim 2(a).

Claim 8 is rejected as being indefinite because the phrase "candidate analog comprising part of said sample" is unclear.

Applicants have amended claim 8 to further clarify the subject matter claimed to obviate this rejection. Applicants submit that all amended claims conform to the second paragraph of 35 USC 112. Reconsideration and withdrawal of the rejection are respectfully requested.

Double Patenting Rejections

The Office Action states that claims 1-5 and 8-10 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over one or more claims of the co-pending U.S. Application 09/267,963.

Applicants are not aware of a co-owned U.S. Patent Application with the above-identified serial number. Clarification is respectfully requested.

Claim rejections under 35 USC §103

Claims 1-5 and 8-10 are rejected under 35 U.S.C. 103(a) as unpatentable over Miyazono (WO 94/11502) in view of Sampath (JBC 267: 20352, 1992), further in view of the Stratagene catalog (1988, p39).

Specifically, Miyazono allegedly discloses the sequences of the subject ALK-2, 3, and 6 TGF-beta superfamily receptors, while failing to teach that the ALKs bind OP-1. Sampath allegedly discloses OP-1 as a TGF-beta superfamily protein. Thus, the Office Action concludes that it would have been obvious to a skilled artisan to screen the receptors of Miyazono using OP-1 as a candidate ligand. Similarly, the Office Action concludes that since the Stratagene catalog teaches several general advantages of using kits in biological research, it would have been obvious to a skilled artisan to arrive at the claimed kit. Applicants respectfully disagree for the reasons which follow.

Pursuant to MPEP 706.02(j), three basic criteria have to be met before a *prima facie* case of obviousness rejection can be made: 1) the prior art references must teach or suggest all the claim limitations; 2) some motivation or suggestion, either found in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references must be present; and 3) a reasonable expectation of success is required.

Applicants have amended claim 1 and added new claims 28, 29 and 31 to clarify the subject matter being claimed. Applicants have also amended claims 2, 8, and their dependent

claims, and added new claim 30 to clarify the subject matter claimed. As amended, claims 1, 28, 29, and 31 are directed to methods and kits for identifying morphogen analogs that bind the recited type-I receptors in the absence of type-II receptors. Claims 2-5, 8, 10, and 30 are directed to methods and kits for identifying OP-1 analogs that elicit an OP-1-mediated cellular response.

Applicants submit that the subject matter of claim 1 (and its related claims) is partly based on the surprising discovery that the OP-1 related morphogens can bind type I receptors (such as the ALK receptors and analogs thereof recited in claim 1) *in the absence* of type II Ser/Thr kinase receptors. This is in contrast to other remotely related TGF-beta superfamily proteins, such as the TGF-beta proteins and activins, which do not bind either type-I or type-II receptors alone, and only bind both type-I and type II receptors in a complex.

For example, the instant specification teaches on page 12, first full paragraph, that the invention contemplates 1) OP-1 or OP-1 analog (morphogen) in specific binding interaction with a type-I receptor (or receptor analog); 2) OP-1 or OP-1 analog (morphogen) in specific binding interaction with a type-II receptor (or receptor analog); and 3) OP-1 or OP-1 analog (morphogen) in specific binding interaction with both a type-I and a type-II receptors. The instant specification further teaches, on page 40 (Example 8) that OP-1 and the related morphogen BMP-4 can bind type-I receptor (ALK-2, -3, and -6) *in the absence* of any type-II receptors.

On the other hand, Miyazono (WO 94/11502) *teaches away* from the claimed invention. Specifically, Miyazono describes the cloning of 6 receptors sharing sequence homology to receptors for TGF-beta superfamily proteins. These receptors were named as "ALK" for "Activin-Like Kinases." Miyazono describes on page 33 that "PAE cells [which only have type I receptors] do not bind activin because of the lack of type II receptors for activin." Miyazono further describes on page 29, lines 26-29, that "[t]ransfection of cDNAs for ALKs into COS-1 cells did not show any appreciable binding of ^{125}I-TGFβ1, consistent with the observation that type I receptors do not bind TGF-β in the absence of type II receptors." Therefore, in view of the fact that the ALK receptors (type I receptors) do *not* bind either TGF-β or activin alone, a skilled artisan would *not* be motivated to screen for other potential ligands of the ALK receptors in the absence of a type II receptor. Thus, even if a skilled artisan had motivation to combine Miyazono and Sampath, the skilled artisan would end up screening for binding of OP-1 or its related ligands to a type I and a type II receptor, and not what is presently claimed. In other words, the

combined teaching would still fail to teach a skilled artisan to screen in the absence of a type II receptor. For the same reason, a skilled artisan would also have no reasonable expectation of success in arriving at the claimed invention. By screening using both receptors, both activin-like ligands and morphogen analogs would be identified. In contrast, the claimed invention (claim 1, etc.) utilizes only type I receptors, and would only identify morphogen analogs.

For the kit claims, the Stratagene catalog, either alone or in combination with any of the other cited references, does not correct any of the above defects. Therefore, all three requirements for establishing a *prima facie* case of obviousness are not met. Reconsideration and withdrawal of the rejection are respectfully requested.

Regarding the second embodiment (OP-1-mediated cellular response), Applicants submit that the claimed invention (represented by claims 2, 8, and their dependent claims) is partly based on the surprising discovery that the ALKs (type I receptors) can participate in the signaling of morphogens such as OP-1. While the idea of screening other TGF-beta superfamily proteins for potential ligands that bind the ALK receptors may be obvious in view of the cited references, the results of such screening are not obvious – otherwise, there would be no need to screen at all. If the results (that is, which of the numerous TGF-beta super family proteins actually bind a particular ALK receptor) are not obvious, then a further method (such as the claimed invention in claim 2) based on a specific result of that experiment (OP-1 binds ALK-2, -3 and -6) is also not obvious. This standpoint is further supported by the disclosure of Miyazono and the instant specification (see Table I on page 40) that certain ALK receptors just cannot bind OP-1 or BMP-4, either in the presence or in the absence of a type II receptor.

In summary, Miyazono and Sampath, either taken alone or in combination, do not teach or suggest that OP-1 actually binds any of the ALK receptors. Thus, the combination of all cited references, assuming *arguendo* they could be properly combined, still would not teach or suggest all the limitations of the instant application. In addition, there is no motivation or suggestion to combine any or all of the above cited references, either in the references themselves or in the knowledge available to a person with ordinary skill in the art at the time of filing. Furthermore, without knowing whether OP-1 binds any of the ALK receptors, there would be no reasonable expectation of success for a skilled artisan to arrive at the claimed invention (identifying OP-1 analog using ALKs) based on the disclosure of the cited references.

Regarding the kit claims, the Stratagene catalog, either alone or in combination with any of the cited references, does not correct any of the above deficiencies. Neither do any of the other cited references (Matsuzaki and the two references by Dijke *et al.*), taken either alone or in combination, correct any of the above-identified deficiencies. Thus, all three requirements for establishing a *prima facie* case of obviousness have not been satisfied. Accordingly, reconsideration and withdrawal of the rejection under 35 USC 103 are respectfully requested.

CONCLUSION

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition therefor and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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